REMARKS

Formal Matters

Claims 1, 2, 4-9, 11-15, 21, 25, 26, 33, 35-37, 41, 42, 57-66, 68, 69, 74-78, 80 are pending in this application. Applicants acknowledge that claim 16 was previously cancelled in an amendment mailed July 26, 2002. Applicants respectfully point out that claim 79 was previously cancelled in an amendment submitted September 26, 2003. Claim 34 is cancelled herewith. Claims are cancelled without prejudice to later prosecution. Claims 33, 61 and 66 are amended herewith. No new matter is added by the amendment as the added recitation is supported throughout the specification such as at page 14, line 7; page 24, lines 34-35; and page 40, lines 24-25; and as found in originally filed, previously pending, now cancelled, claim 34.

In view of the Examiner's earlier restriction and species election requirements, it is Applicant's understanding that upon the allowance of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application, and that and upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. Further, applicant retains the right to present withdrawn claims in a divisional application.

Withdrawal of Objections and Rejections

Applicants gratefully acknowledge withdrawal of objections and rejections as stated on pages 2-4 of the Office Action mailed February 20, 2004.

REJECTIONS MADE ON ALLEDGED NEW GROUNDS

Rejection Under 35 U.S.C. § 102(b) (Alderson et al.)

Claims 1, 2, 4, 8, 9, 12-15, 33, 36, 41, 42, 61-63, 66, 68, 75, 76, 77, 78, 80, 86, 75, and 76 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Alderson et al. (International Immunology, 6:1799-1806 (1994)). Applicants respectfully traverse the rejection

as applied and as it might be applied to the currently pending claims for the reasons provided below.

Before presenting arguments, Applicants respectfully note that the recitation of features in the claims is incorrect at line 7 of the third paragraph on page 5: "claims 8, 33" should read "claims 8, 36" as claims reciting at least two light chain variable domain polypeptides.

Applicants' independent claims are drawn to an isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region (independent claim 1); an isolated antibody comprising three or more antigen binding sites wherein the antibody is not an IgM or IgA antibody and the antibody is capable of binding a receptor in the TNF superfamily (claim 33); a polypeptide comprising VH/CH1 domains as recited in claim 57; and an isolated antibody comprising a dimerization domain and three or more antigen binding sites amino-terminal thereto; a polypeptide chain comprising three or more light or heavy chain variable domains forming three or more antigen binding sites each directed against the same antigen, wherein the polypeptide chain is not a native IgM or IgA antibody (claim 66). In a previous, second, restriction requirement, Applicants responded on November 18, 2002 and elected claims 1-15, 21-26, 33-42, 57-69, and 73-80, drawn to an antibody that binds to DR5 and a conjugated antibody to cytotoxic agent. Applicants elected Species 2 for claims 5-10, 57-68 and 73-79 (the different structures in VDs, number of amino acids in X positions, VH and CH linking patterns). The Examiner later made a species election requirement, to which Applicants responded on January 9, 2003 and elected the species "four antigen binding sites," the VH-CH1-VH-CH1 Fc region, and the gly-ser-gly-ser amino acid linker in claim 11.

Alderson et al. disclose an anti-Fas IgM antibody (see page 1800 of Alderson et al.). The authors do not disclose an isolated antibody comprising an Fc region wherein three or more antigen binding sites are amino terminal to the Fc region. A native IgM antibody contains an Fc region and multiple antigen binding regions, but there is only one or two antigen binding region(s) amino-terminal to an Fc region, not three or more as Applicants claim or the four antigen binding sites of the claimed elected species.

The Alderson et al. reference fails to disclose each and every element of Applicants' claims and, as a result, does not anticipate Applicants' claimed invention. The rejection should be withdrawn, which action is respectfully requested.

With respect to claim 12, the Examiner asserts that the Office lacks facilities to provide factual evidence to establish the composition of the prior art. With respect, the Examiner's comments are moot based on Applicants' argument above. Claim 12, being dependent from claim 1, is not anticipated by the Alderson et al. reference for the reasons provided above for claim 1. Specifically, the isolated antibody of claim 1 (and dependent claim 12) comprises three or more antigen binding sites amino-terminal of an Fc region, which is not the case for the IgM antibody of Alderson et al. The rejection of claim 12 should be withdrawn as well, which action is respectfully requested.

Applicants respectfully submit that the rejection under Section 102(b) has been overcome and request withdrawal of the rejection and allowance of the claims.

Rejection Under 35 U.S.C. § 103(a) (Zapata in view of Shu)

Claims 1, 2, 4-9, 12-15, 57-66, 68 and 74-78 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zapata et al (1995, Protein Engineering, vol. 8, pages 1057-62, primary reference) in view Shu et al (1993, Proc. Natl. Acad. Sci. USA, vol. 90, pages 7995-9, secondary reference). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants' invention as a whole: Applicants' claimed invention is, in part, an isolated antibody comprising three or more antigen binding sites that in not a native IgM or IgA or having the three or more antigen binding sites amino-terminal to an Fc region. Applicants elected certain species, as described above.

Zapata et al. disclose "linear antibodies" comprising a pair of tandem Fd segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a bivalent antibody fragment having a pair of antigen binding regions. Zapata et al. do not contemplate or disclose an antibody having an Fc region and four (or even three or more) antigen binding sites amino terminal of the Fc region; or an antibody having a dimerization domain and four (or even three or more) antigen binding regions amino-terminal thereto; or a polypeptide having four (or

even three or more) heavy or light chain variable domains forming four (or three or more) antigen binding sites.

Shu et al. describe construction of a single-chain immunoglobulin-like molecule having one heavy chain and one light chain variable domain of a monoclonal antibody joined via a linker while the carboxyl end of the variable light chain was liked to the amino terminus of an Fc region, where each single chain is assembled into a dimeric molecule having two antigen binding sites (see the abstract).

Neither Zapata et al. nor Shu et al. contemplate, much less disclose, an isolated antibody as claimed by Applicants having four antigen (or even three or more) binding sites. The combination of Zapata et al. and Shu et al. cannot add what is not found in either reference: namely, the presence of four (or three or more) antigen binding regions amino terminal to an Fc or a dimerization region. Such an antibody would not have been obvious to one of ordinary skill in the art reading the cited references because such a teaching was not available prior to Applicants' disclosure. Applicants respectfully submit that it is only through impermissible use of hindsight available only through reference to Applicants' patent disclosure that the Examiner has crafted the rejection. There is no teaching or motivation in the literature to generate an antibody having four (or three or more) antigen binding sites amino-terminal to an Fc or a dimerization region.

Applicants respectfully submit that the rejection under Section 103(a) is improper because of the use of impermissible hindsight and should be withdrawn, which action is requested.

Rejection Under 35 U.S.C. § 103(a) (Zapata in view of Shu and WO98/41629)

Claims 1, 2, 4-9, 12-15, 57-66, 68 and 74-78 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zapata et al (supra) in view Shu et al (supra) and further in view of WO98/41629. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

The non-obviousness of Applicants' invention in view of rejection over the Zapata and Shu references is stated above.

WO98/41629 discloses DR5, the antigen species elected by Applicants. The addition of the particular antigen to which an antibody of Applicants' invention may bind fails to cure the deficiency of the Zapata and Shu references discussed above. The deficiency is the absence of any suggestion or teaching in Zapata or Shu of an antibody having four (or three or more) antigen binding sites amino-terminal of an Fc region or a dimerization region. The teaching of the particular antigen to which a bivalent antibody (of the Zapata and/or Shu references) binds does not yield an antibody having four (or three or more) antigen binding sites to DR5 or to any antigen.

The rejection remains improper through the use of impermissible hindsight, which error is not cured by the rejection further in view of WO98/41629. As a result, the rejection should be withdrawn, which action is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (Zapata in view of Shu and Paprocka)

Claims 1, 2, 4-9, 12-15, 57-66, 68 and 74-78 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zapata et al (supra) in view Shu et al (supra) and further in view of Paprocka, M. et al. (Arch Immunol. Ther Exp (Warsz). 40(3-4):223-227 (1992) abstract). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

The non-obviousness of Applicants' invention in view of rejection over the Zapata and Shu references is stated above. In this rejection, the Examiner further interprets the claims to be drawn to an antibody linked to a cytotoxic agent.

Paprocka et al. disclose linking ricin (a cytotoxic agent) coupled to a monoclonal antibody. Such a teaching fails to cure the deficiency of the Zapata and Shu references are argued above. The absence of a teaching of four (or three or more) antigen binding sites amino-terminal to an Fc region or a dimerization region of an antibody is the deficiency of the Zapata and Shu references alone or in combination. The teaching of a linked cytotoxic agent by Paprocka et al. does not cure this deficiency.

Applicants respectfully submit that the rejection under Section 103(a) remains improper as being based on the impermissible use of hindsight. The rejection should be withdrawn, which action is respectfully requested.

SUMMARY

Claims 1, 2, 4-9, 11-15, 21, 25, 26, 33, 35-37, 41, 42, 57-66, 68, 69, 74-78, 80 are pending in the application. Claim 34 is canceled without prejudice to later prosecution.

Claims 33, 61, and 66 are amended without the addition of new matter. The rejections under Sections 102(b) and 103(a) have been overcome. Withdrawal of the rejections and allowance of the claims is respectfully requested.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

GENENTECH, INC.

Date: August 17, 2004

By: _____

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Apendix

1. (Original) An isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region.
2. (Original) The antibody of claim 1 comprising four antigen binding sites.
3. (Cancelled)
4. (Original) The antibody of claim 1 comprising a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.
5. (Original) The antibody of claim 4 wherein the polypeptide chain comprises VD1-$(X1)_n$-VD2-$(X2)_n$-Fc, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1.
6. (Original) The antibody of claim 5 comprising two or more polypeptide chains, each comprising VD1-$(X1)_n$-VD2-$(X2)_n$-Fc.
7. (Original) The antibody of claim 1 comprising at least one polypeptide chain with the formula:
   (a) VH-CH1-flexible linker-VH-CH1-Fc region chain; or
   (b) VH-CH1-VH-CH1-Fc region chain.
8. (Original) The antibody of claim 1 comprising at least two light chain variable domain polypeptides.
9. (Original) The antibody of claim 8 wherein the light chain variable domain polypeptides further comprise a CL domain.
10. (Cancelled)
11. (Once Amended) The antibody of claim 7 wherein the flexible linker comprises the peptide gly-ser-gly-ser (SEQ ID NO:10).
12. (Original) The antibody of claim 1 which is internalized faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind.
13. (Original) The antibody of claim 1 which is an agonist antibody.
14. (Original) The antibody of claim 1 which induces apoptosis.

15. (Original) The antibody of claim 1 wherein the three or more antigen binding sites all bind the same antigen.
16. (Cancelled)
17. (Cancelled)
18. (Cancelled)
19. (Cancelled)
20. (Cancelled)
21. (Once Amended) The antibody of claim 1 which binds a DR5 receptor.
22. (Cancelled)
23 (Cancelled)
24. Cancelled)
25. (Original) The antibody of claim 21 which is an agonist antibody.
26. (Original) The antibody of claim 21 which induces apoptosis.
27. (Cancelled)
28. (Cancelled)
29. (Cancelled)
30. (Cancelled)
31. (Cancelled)
32. (Cancelled)
33. (Once Amended) An isolated antibody comprising three or more antigen binding sites, wherein the antibody is not a native sequence IgM or IgA antibody and is capable of binding a receptor in the Tumor Necrosis Factor (TNF) receptor superfamily.
34. (Cancelled)
35. (Original) The antibody of claim 33 which has only one Fc region or lacks an Fc region.
36. (Original) The antibody of claim 33 which comprises a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.
37. (Original) The antibody of claim 33 which comprises four antigen binding sites each capable of binding the DR5 receptor.
38. (Cancelled)

39. (Cancelled)

40. (Cancelled)

41. (Original) The antibody of claim 33 which is an agonist antibody.

42. (Original) The antibody of claim 33 which induces apoptosis.

43. (Cancelled)

44. (Cancelled)

45. (Cancelled)

46. (Cancelled)

47. (Cancelled)

48. (Cancelled)

49. (Cancelled)

50. (Cancelled)

51. (Cancelled)

52. (Cancelled)

53. (Cancelled)

54. (Cancelled)

55. (Cancelled)

56. (Cancelled)

57. (Once Amended) A polypeptide chain comprising:

(a) VH-CH1-flexible linker-VH-CH1-dimerization domain; or
VH-CH1-VH-CH1-dimerization domain; and
wherein the dimerization domain comprises an Fc region.

58. (Original) An isolated antibody comprising the polypeptide chain of claim 57.

59. (Original) The antibody of claim 58 further comprising two or more light chain variable domain polypeptides.

60. (Original) The antibody of claim 59 wherein the light chain variable domain polypeptides comprise VL-CL.

61. (Twice Amended) An isolated antibody comprising a dimerization domain and three or more antigen binding sites amino-terminal thereto, wherein the antibody is not a native sequence IgM or IgA antibody.

62. (Original) The antibody of claim 61 wherein the dimerization domain is selected from the group consisting of a hinge region, an Fc region, a CH3 domain, and a CH4 domain.

63. (Original) The antibody of claim 62 wherein the dimerization domain is a hinge region.

64. (The antibody of claim 63 wherein the dimerization domain further comprises a leucine zipper.

65. (Original) The antibody of claim 63 comprising a polypeptide chain comprising the formula:

(a) VH-CH1-flexible linker-VH-CH1-hinge region; or

(b) VH-CH1-VH-CH1-hinge region.

66. (Once Amended) A polypeptide chain comprising three or more heavy chain or light chain variable domains, wherein each of the variable domains is able to combine with three or more light chain or heavy chain variable domain polypeptides to form three or more antigen binding sites, each directed against the same antigen and wherein the antibody is not a native sequence IgM or IgA antibody.

67. (Cancelled)

68. (Original) The polypeptide chain of claim 66 which comprises four heavy chain variable domains which are able to combine with four light chain variable domain polypeptides to form four antigen binding sites directed against the same antigen.

69. (Once Amended) The polypeptide chain of claim 66 wherein the antigen is a DR5 receptor.

70. (Cancelled)

71. (Cancelled)

72. (Cancelled)

73. (Cancelled)

74. (Once Amended) The polypeptide chain of claim 68 comprising the formula:

(a) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1;

(b) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1; or

(c) $(VH\text{-}CH1)_n$, wherein n is three or four.

75. (Original) An isolated antibody comprising the polypeptide chain of claim 66.

76. (Original) The isolated antibody of claim 75 further comprising the three or more light chain or heavy chain variable domain polypeptides.

77. (Original) The isolated antibody of claim 76 comprising three or more light chain variable domain polypeptides, each comprising VL-CL.

78. (Original) The isolated antibody of claim 77 comprising four light chain variable domain polypeptides, each comprising VL-CL.

79. (Cancelled)

80. (Original) An immunoconjugate comprising the antibody of claim 75 conjugated with a cytotoxic agent.

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